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REVIEW

New developments in the management of COPD: clinical utility of indacaterol 75 µg

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Abstract: Chronic obstructive pulmonary disease (COPD) is a global health challenge and a major cause of mortality worldwide. Bronchodilators, particularly long-acting β_2-agonists and long-acting antimuscarinic agents, used singly or in combination, aim to improve lung function, reduce symptoms, prevent exacerbations, and enhance quality of life of COPD patients. Indacaterol is a novel, inhaled, long-acting β_2-agonist, with rapid onset of action and once-daily dosing providing 24-hour bronchodilation. Currently, the recommended dose differs between Europe (150 µg; maximum 300 µg) and USA (75 µg), the latter is lower than that assessed in the majority of the conducted studies. This review summarises published evidence regarding the efficacy, tolerability, and safety of indacaterol at a dose of 75 µg. Indacaterol 75 µg was found to be superior than placebo regarding lung function, dyspnea, health status, use of rescue medication, and rate of exacerbations. Furthermore, indacaterol 75 µg was well tolerated, while the most frequent adverse effect was deterioration of COPD occurring at a frequency similar to placebo, without major cardiovascular adverse effects. In conclusion, indacaterol 75 µg, administered once daily, is efficacious and has an excellent tolerability and safety profile, and is therefore a valid alternative in the treatment of COPD patients.

Keywords: chronic obstructive pulmonary disease, long-acting bronchodilators, β_2-agonists, indacaterol

Definition and management of COPD

Chronic obstructive pulmonary disease (COPD) is a common preventable disease, characterized by persistent airflow limitation, which is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[1] COPD is a major clinical issue globally, as it affects approximately 10% of the population aged over 40 years old, and its prevalence is estimated to increase in the next decade.[2] It also represents one of the leading causes of morbidity and mortality worldwide, and estimates suggest that it will become the fourth leading cause of death by the year 2030.[3,4] Tobacco smoking is the major risk factor for the development and progression of the disease, followed by occupational exposure and air pollution; thus, smoking cessation combined with pharmacologic and non-pharmacologic treatment may affect disease course and progression.[1,5] COPD is also associated with increased economic burden, mainly due to its acute exacerbations.[6]

The cardinal pathogenic feature of COPD is airflow obstruction, associated with an enhanced chronic inflammatory response that results in a combination of airway disease and lung parenchyma destruction.[1] As disease progresses, the patient's lung function and health status deteriorate with increasing disability and decreasing exercise tolerance.[1]

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Symptoms include dyspnea, cough, sputum production, wheezing, and chest tightness. Diagnosis is essentially based on patients' history of exposure to risk factors and spirometric evaluation, showing a fixed post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity of less than 0.7.[1]

To date, there is no effective pharmacologic treatment that reduces the mortality or decreases the rate of decline of lung function in COPD. The main goals of pharmacotherapy are: 1) reduction of symptoms, particularly breathlessness; 2) improvement of exercise capacity and 3) prevention of exacerbations, in order to enhance health status and quality of life.[1,7] Non-pharmacological therapeutic options include smoking cessation, rehabilitation, oxygen therapy, and surgical treatments.[1,8,9]

A multi-component staging system for COPD severity has been developed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) that categorizes disease severity based on: 1) the severity of airflow limitation (FEV_1 percent predicted), 2) risk of exacerbations, and 3) symptoms (based on modified Medical Research Council dyspnea scale or COPD Assessment Test).[1] GOLD recommends that treatment should be regulated according to disease severity, and medications should be added in a stepwise and cumulative manner as disease advances.[1]

Bronchodilators play a central role in the treatment of COPD. Short-acting bronchodilators are essential in symptom relief and can be used as needed, independently of disease severity.[1] Long-acting inhaled β_2-agonist bronchodilators, such as salmeterol, formoterol, and anticholinergic agents such as tiotropium, or different combinations, are indicated as maintenance therapy for patients with moderate or more severe disease.[1,10] Inhaled corticosteroids, are recommended as supplementary therapy to long-acting inhaled β_2-agonist bronchodilators for patients in severe or very severe stage and a history of frequent exacerbations.[1]

Indacaterol is a novel, inhaled, long-acting β_2-agonist bronchodilator, approved in 2009 at doses of 150 and 300 μg once daily by the European Medicines Agency (EMA) for maintenance bronchodilator treatment of airflow obstruction in patients with COPD. In July 2011, the US Food and Drug Administration (FDA) permitted its use in the USA with the same indication (maintenance therapy of airflow obstruction in COPD patients) at a lower recommended dose of 75 μg.[11] Indacaterol has a fast onset of action (5 minutes) and a longer duration (24 hours) than the other long-acting β_2-agonists, properties conferred by its unique biochemical structure,[12] and hence is defined as "ultra-long-acting β_2-agonist."[13] Various clinical studies have assessed the safety and tolerability profile of indacaterol. Additionally, results from multiple studies, investigating indacaterol's efficacy, demonstrate an increase in lung function indices, amelioration of patients' symptoms, improvement of health status, reduction of use of rescue medication, and decrease of exacerbation rate in comparison with placebo.[14–16] When compared with alternative bronchodilators, indacaterol improved indices of lung function equally to tiotropium and in a higher degree than salmeterol and formoterol.[17,18]

The purpose of this review is to summarize current knowledge regarding the efficacy, safety, and tolerability of inhaled indacaterol, emphasizing the dosage scheme approved by the FDA (75 μg). Our search focused on the following databases: PubMed, EMBASE, and Google Scholar, using combinations of the following keywords: indacaterol 75 μg, COPD, bronchodilators, and β_2-agonists. The search included all types of articles written in English, published up to July 2013.

Pharmacokinetic and pharmacodynamic profile of indacaterol

Indacaterol is a chirally pure β_2-adrenoreceptor agonist that exerts its activity by provoking relaxation of airway smooth muscle through adenylate cyclase stimulation, which in turn catalyzes the production of intracellular cyclic adenosine monophosphate.[19] An additional therapeutic benefit may include mast cell stabilization, since in-vitro indacaterol inhibited immunoglobulin E-dependent release of mediators from human lung mast cells in a concentration-dependent manner.[20]

Functional data indicates indacaterol as a partial agonist; however, in comparison to isoprenaline, it presents a nearly complete affinity for the human β_2-adrenoreceptor and a greater affinity compared with salmeterol (E_{max}=73%±1% versus 38%±1%).[19,21] Similar to formoterol, indacaterol has a weak relative affinity at the β_1-adrenoreceptor and is a full agonist at the β_3-adrenoreceptor.[19] When compared with salbutamol or salmeterol, indacaterol demonstrates a twofold higher intrinsic activity, therefore presenting a decreased antagonistic action at the β_2-adrenoreceptor.[19] In the study of Sturton et al,[22] indacaterol and formoterol presented a similar intrinsic efficacy, followed by albuterol and salmeterol. These characteristics may explain the absence of tachyphylaxis[19] as well as the lack of an antagonistic effect with short-acting β_2-adrenoreceptor agonists.[21]

After inhalation, indacaterol is rapidly absorbed into the systemic circulation, reaching peak serum levels at a median time of 15 minutes.[23] Two studies conducted on human airways investigated the effects of indacaterol. In the first study, indacaterol demonstrated an onset of action similar to that of formoterol (7.8±0.7 minutes versus 5.8±0.7 minutes respectively) but significantly faster in comparison to salmeterol (19.4±4.3 minutes), while duration of action was longer than both formoterol and salbutamol (>12 hours versus 35.3±8.8 minutes and 14.6±3.7 minutes respectively).[21] In the second study, there was a rapid onset of action for albuterol (1.6±0.3 minutes), formoterol (2.0±0.3 minutes), and indacaterol (3.0±0.2 minutes) and significantly slower for salmeterol (6.6±0.3 minutes, $P<0.05$), while indacaterol and salmeterol presented longer duration of action in comparison to albuterol and formoterol.[22] The rapid effect of action does not depend on the time of administration (morning or evening).[24] Fast onset of action and sustained duration may be attributed to the high affinity for lipid raft domains within the membrane.[25] Higher partitioning of indacaterol into the receptor microenviroment and its faster membrane permeation may also contribute.[26]

The absolute bioavailability after inhalation is on average 43%. Indacaterol is detectable in serum at a dose-dependent concentration, and a slight accumulation occurs after administration of multiple daily doses, with a steady state achieved within 12–14 hours of treatment. Biliary exertion is the main route of elimination for indacaterol and its metabolites.[14]

Efficacy

FEV_1

Indacaterol 75 µg versus placebo

Trough FEV_1 (ie, FEV_1 at the end of the dosing interval) is a physiological variable commonly used in the studies evaluating the effects of long-acting bronchodilators. An increase in trough FEV_1 between 100 and 140 mL is considered significant and has been shown to be associated with improvements of health status in COPD patients treated with bronchodilators.[27,28]

Kerwin et al[29] investigated the efficacy of indacaterol at a dose of 75 µg in two randomized, double-blind, placebo-controlled studies of similar design for a total time of 12 weeks in 641 COPD patients. In both studies, at the end of the study period, indacaterol showed superiority compared with placebo, with increases in trough FEV_1 of 120 mL (95% confidence interval [CI], 80–150 mL; $P<0.001$) in the first and 140 mL (95% CI, 100–180 mL; $P<0.001$) in the second study respectively. Further analyses demonstrated improvements in trough FEV_1 independently from albuterol reversibility and increases more than 100 mL in all subgroups investigated.

Regarding the onset of action, at 5 minutes after the first dose, trough FEV_1 of patients receiving indacaterol showed a difference of 90 mL (95% CI, 70–100 mL; $P<0.001$) in the first, and 100 mL (95% CI, 80–120 mL; $P<0.001$) in the second study compared with placebo, while the difference after the first dose was 80 mL for both studies (95% CI, 60–100 mL and 50–110 mL respectively; both $P<0.001$) compared with placebo. Additionally, the maximum effect on trough FEV_1 over placebo was observed nearly 1–2 hours after dosing, with an increase of approximately 170–190 mL. The authors have noted that differences in trough FEV_1 between the two studies were probably due to younger age of patients included in study 2 and less severe disease stage, resulting in greater FEV_1 variability.

In another study by Barnes et al, using an adaptive seamless design,[30] which included a total of 801 COPD patients, the preset efficacy criterion after 15 days was satisfied by all doses, including that of 75 µg. Results from a patient level network meta-analysis[31] also confirmed the superiority of indacaterol compared with placebo regarding FEV_1 at 12 weeks.

Indacaterol at a dose of 75 µg has been proven to be more effective than placebo in terms of lung function. Similar conclusions were obtained from studies when higher doses were considered.[32–34] However, indacaterol at doses of 150 and 300 µg showed greater FEV_1 improvements in comparison to the minimum dose, with good tolerance profile.[35]

Indacaterol 75 µg versus other bronchodilators

Currently, there are no studies comparing directly the efficacy of indacaterol at the dose of 75 µg with other available bronchodilators. Cope et al[36] performed a network meta-analysis that included 15 studies in order to investigate the efficacy of indacaterol once daily in comparison to fixed-dose combinations of formoterol/budesonide (FOR/BUD); and salmeterol/fluticasone (SAL/FP). When data was unadjusted for covariates, indacaterol 75 µg presented an increase from baseline FEV_1 at 12 weeks compared with FOR/BUD 9/160 µg of 0.09 L (95% credible interval [CrI], 0.04–0.13) and compared with FOR/BUD 9/320 µg of 0.07 L (95% CrI, 0.03–0.11). When indacaterol 75 µg was compared with SAL/FP 50/250 µg, no difference from baseline was noted (95%CrI, –0.07–0.07), while in comparison with SAL/FP 50/500 µg, baseline FEV_1 increased by 0.01 L (95% CrI, –0.04–0.05). Researchers concluded that indacaterol at a dose of 75 µg demonstrated a similar efficacy as FOR/BUD and a comparable efficacy as SAL/FP, all doses considered.

In another network meta-analysis,[31] the efficacy of indacaterol 75 μg once daily was compared with tiotropium 18 μg, salmeterol 50 μg, formoterol 12 μg, and placebo. All treatments were superior to placebo, and indacaterol was estimated to present equal efficacy, in terms of FEV_1 at 12 weeks, to tiotropium and salmeterol, while demonstrating higher FEV_1, compared to formoterol.

All results considered, indacaterol at the dose of 75 μg presents comparable efficacy to well established medications, offering a new valid alternative for the treatment of COPD patients.

Dyspnea

Transition dyspnea index (TDI) is a well validated tool that reflects the changes of dyspnea severity from baseline. A difference of ≥1 as the minimum clinically important difference (MCID) was used to express dyspnea variability.[37]

The effects of indacaterol at a dose of 75 μg on dyspnea were investigated as the secondary endpoint in two identically designed double-blind, placebo-controlled studies.[38] Results showed that treatment with indacaterol improved dyspnea, as expressed by the TDI total score, in both studies in comparison to placebo at week 4 and only in one study at week 12, with mean TDI scores for the indacaterol and placebo groups 1.34 (standard error [SE] 0.284) and 0.11 (SE 0.287) in the first study and 1.22 (SE 0.234) and 0.76 (SE 0.235) in the second study, respectively. When compared with placebo, the first study produced results that approximated (0.97 [95% CI, 0.39–1.55] at week 4) or exceeded (1.23 [95% CI, 0.57–1.89] at week 12) the MCID. A meta-analysis, performed by Han et al,[15] combined the two abovementioned studies. Odds ratio estimates from individual studies varied from 1.582 to 2.015, while overall odds ratio estimate was 1.784 (95% CI, 1.282–2.482), with no evidence of heterogeneity (P=0.474, I^2=0.000), demonstrating that patients treated with indacaterol were more prompt in achieving the MCID after 12 weeks of therapy. The percentage of patients achieving a TDI score ≥1 was 48% compared with 34% for those receiving placebo.

In a network meta-analysis,[36] indacaterol 75 μg demonstrated lower TDI scores when compared with SAL/FP 50/500 μg (difference −0.49 [95% CI, −1.87–0.89]). However, results were considered inconclusive by the authors, while comparison with FOR/BUD and SAL/FP 50/250 μg was not possible due to lack of data.

Health status

The St George's Respiratory Questionnaire (SGRQ) is a valid measure of impaired health and has been shown to correlate well with symptoms level, disease activity, and disability.[39] Gotfried et al[38] reported results from two studies where health status was considered as a secondary endpoint. SGRQ was used to evaluate health status variability, and a cutoff of ≥4 units to baseline, represented the MCID. Treatment with indacaterol improved health status, as assessed by SGRQ, compared with placebo in all sectors (symptoms −8.8 [standard deviation (SD) 17.78] and −8.5 [SD 17.86], activity −5.7 [SD 13.84] and −4.3 [SD 16.01], and impacts −4.8 [SD 12.84] and −4.2 [SD 15.63]). Treatment with indacaterol, in comparison to placebo, was associated with increased ability to perform activities, more symptom-free days, and less use of salvation therapy. On the other hand, number of nights with sleep without waking did not significantly differ between indacaterol treatment and placebo.

When compared with other bronchodilators through network meta-analysis, indacaterol 75 μg presented a similar effect on health status as tiotropium and formoterol, and an augmented efficacy in comparison to salmeterol.[31]

Exacerbations

COPD exacerbation is defined as an acute worsening of symptoms that is beyond daily variation and results in treatment modification.[1] Exacerbations represent crucial points in the disease course, as they have negative effects on symptoms, lung function, and health status, and increase both morbidity and mortality.[1]

In the studies of Kerwin et al,[29] number of exacerbations was considered as an exploratory endpoint. Important limitations of the studies include the short duration (12 weeks), the parameters evaluated, (ie, mainly symptoms and lung function), as well as the entry criteria (patient history and risk of exacerbation was not considered). However, the number of exacerbations was low in both studies.[40]

Donohue et al,[41] in order to evaluate the rate of exacerbations compared with placebo, used pooled data from 445 COPD patients treated with indacaterol 75 μg. Frequency of exacerbation was reduced compared with placebo (P=0.0325), and no significant differences between treatments were observed.

Use of rescue medication

Short-acting β_2-agonist bronchodilators are recommended as rescue therapy in all COPD stages and the frequency of their use indirectly reflects disease status.[1] In the studies of Kerwin et al[29] use of rescue albuterol was investigated as secondary endpoint. Patients receiving indacaterol showed a decrease in the use of rescue therapy by 1.2 and 0.7 puffs

per day ($P<0.001$) and also used albuterol less frequently (13.7%–8.4% fewer days, $P<0.01$) compared with those treated with placebo.

Safety and tolerability of indacaterol

In the two placebo-controlled, 12-week studies performed by Kerwin et al,[29] serious adverse events occurred in 2.5% in the indacaterol group (75 µg) and in 5.6% and 2.5% of the patients treated with placebo. The most important adverse event described, was COPD worsening, which occurred at a frequency of 9% in patients receiving indacaterol and 12% and 8% in the placebo groups. Minor adverse effects included headache (6% and 3% of cases in the first and second study, respectively) and nasopharyngitis (5% and 6% of cases in the first and second study, respectively). Cough was more frequent between patients treated with indacaterol in the study 2 compared with placebo (9.4% versus 3.1%) and presented similar frequency in study 1 (4.3% versus 4.4%); while symptoms associated with β_2-adrenoreceptor stimulation were infrequent (<2%).

Donohue et al[41] have pooled data from 449 patients with moderate-to-severe COPD treated with double-blind indacaterol at different doses, including that of 75 µg. Most common adverse events included COPD worsening, nasopharyngitis, and headache, with a relative risk of 0.66 (95% CI, 0.47–0.93), 1.52 (95% CI, 0.94–2.46), and 2.34 (95% CI, 1.46–3.76), respectively. Other adverse events included infections, musculoskeletal disorders, and effects related to β_2-adrenoreceptor stimulation, all with limited effects on the safety profile. Analysis regarding major adverse cardiovascular events showed a decrease in the incidence for all active treatments in comparison to placebo. No deaths occurred in the indacaterol group at a dose of 75 µg and, compared with placebo, the relative risk of death was reduced in the active treatment group for all doses. Moreover, in the 2-week adaptive seamless study conducted by Barnes et al, no safety issues occurred, and no relation to treatment doses was observed.[30]

Indacaterol, at the dose of 75 µg, was well tolerated and showed a good overall safety profile, while differences between treatment groups in terms of cardiovascular and biochemical variables were clinically irrelevant.

Conclusion

Indacaterol is a novel, ultra-long-acting β_2-bronchodilator, with a rapid onset of action, 24-hour duration, and an effect that is sustained for up to 1 year in long-term treatment.[42] The results of studies examining efficacy showed a beneficial effect in terms of FEV_1 improvement, dyspnea, health status, use of salvation therapy, and frequency of exacerbations.[14,43] These characteristics, along with the once-daily administration scheme, may improve adherence to therapy, thus rendering indacaterol as an optimal therapy for COPD, either alone or in conjunction with other bronchodilators. Moreover, in two cost-utility analyses, indacaterol proved to be more cost-effective, compared with salmeterol and tiotropium, mainly due to a lower total cost and better outcomes relationship.[44,45]

The approved dose of indacaterol in the USA (75 µg once daily) is lower than the one approved in Europe (either 150 or 300 µg).[11] The impact of the different dosages of this medication on long-term outcomes remains unknown. Indacaterol at a dose of 75 µg has been demonstrated to provide benefits comparable to higher doses in terms of safety, efficacy, and tolerability. Even though these results were mainly based on studies of limited duration (12 weeks)[31] and data regarding long-term treatment are lacking, longer duration studies conducted with higher doses showed that indacaterol presents good bronchodilator efficacy without evidence of tolerance.[16] Unfortunately, to date there are no randomized, controlled trials comparing the efficacy between indacaterol 75 µg and higher dosage schemes.

In addition, to date, there are no data available on the effect of indacaterol 75 µg on hyperinflation, an important feature of COPD, and on exercise capacity. However, previous studies on higher doses of the drug have demonstrated improvement on resting and dynamic air trapping, as well as a beneficial effect on exercise tolerance.[46,47]

Available evidence also suggests that indacaterol demonstrates a similar/better efficacy profile in comparison with other bronchodilators.[19] Based on two identically designed double-blind 12-week studies, the combination of indacaterol at a higher dose of 150 µg with tiotropium could yield greater bronchodilation and improvement on lung deflation than tiotropium alone.[48] Moreover, van Noord et al[49] assessed the efficacy of the long-acting muscarinic antagonist glycopyronium combined with indacaterol 300 µg and showed significant improvements in terms of lung function in comparison with indacaterol alone or placebo. Thus, studies investigating new treatment options, including combinations of indacaterol at lower doses with other bronchodilators, should be instituted in order to evaluate their effects on the different aspects of COPD.

Regarding safety, pooled data analysis from clinical studies shows an overall similar incidence of adverse events

between various doses.[41] No fatal cases in patients receiving indacaterol 75 µg were reported.

In summary, available data suggest that indacaterol 75 µg presents a good safety and tolerability profile. However, short patient follow-up is an important limitation. Although long-term data is not yet available, studies with higher doses and major duration (up to 1 year) have shown that indacaterol is safe and well tolerated in the treatment of COPD.[34,42,50]

Disclosure

The authors report no conflicts of interest in this work.

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